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GOSAVI, Arun, S. [IN/IN]; "Bhakti" C-31, N4, Cidco,  
New Aurangabad 431 003, Maharashtra (IN).

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(71) Applicant (for all designated States except US): WOCK-  
HARDT LIMITED [IN/IN]; Wockhardt Towers, Bandra  
Kurla Complex, Bandra (East), Mumbai 400 051 (IN).

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(72) Inventors; and

(75) Inventors/Applicants (for US only): HUSSAIN, Javed  
[IN/IN]; Plot No. 8, N8 Cidco, Azad Chowk, Aurangabad  
431 003, Maharashtra (IN). KHAPRA, Pankaj [IN/IN];  
14, Pal Apartments, N-2 Cidco, Aurangabad, 431 003 (IN).



**WO 03/037304 A1**

(54) Title: CONTROLLED RELEASE COMPOSITIONS FOR MACROLIDE ANTIMICROBIAL AGENTS

(57) Abstract: The present invention provides a controlled release pharmaceutical composition of an acid labile, poorly soluble drug having pH dependent solubility profile in aqueous environment. In a preferred embodiment the drug is combined with a practically water insoluble polymer an optimizing agent and optional additives to produce a controlled release of therapeutic agent when compositions is exposed to aqueous environment.

CONTROLLED RELEASE COMPOSITIONS FOR  
MACROLIDE ANTIMICROBIAL AGENTS

5

Cross-Reference to Related Application

This application claims priority from U.S. Provisional Patent Application No. 60/338,234, filed: November 02, 2001, which is incorporated herein by reference.

10

BACKGROUND OF INVENTION

Controlled drug delivery devices offer clinically significant advantages for various therapeutically active agents by way of increasing patient compliance due to reduced frequency of administration, improve the safety and efficacy of drug substances and reduce undesirable effects in comparison to the 15 corresponding immediate release dosage form. The advantages of controlled release or sustained release or modified release products are well known in the pharmaceutical field.

Many such drug delivery devices are commercially available and are produced by various technologies known in the art. However, some of these 20 technologies require special processes and equipment for production. In addition, some of these systems have limited applications because their ability to produce a desired release profile of a therapeutic agent depends upon several factors, *e.g.*, the physico-chemical properties of therapeutic agent, additives in the drug delivery device, physiological factors and the like. The object of a 25 controlled drug delivery device or composition is to limit, control or modify (*e.g.*, slow) the drug release characteristics relative to an immediate release system of the same drug. While, many controlled release formulations are already known, certain moderately to poorly soluble or practically insoluble drugs present formulation difficulties and cannot be successfully formulated as a 30 controlled drug delivery device employing these formulation techniques. In addition, due to variability in physico-chemical characteristics of the therapeutic agent, variation in their response in the body upon administration and variation

in their response on combining with additives, some of the existing technologies are inadequate. The emergence of newer therapeutic agents and understanding of pharmacokinetics and physiological needs make the task of controlled drug delivery more complex.

5        Clarithromycin is a 14-membered macrolide antimicrobial agent that exhibits a broad spectrum of antimicrobial activity against gram-positive and gram-negative pathogens making it suitable for numerous clinical situations demanding antibacterial agents. Depending on the pharmacokinetic characteristics, antibacterial agents may be administered orally more than once  
10      per day to maintain a minimum effective concentration throughout the day and night. However, a more desirable dosage regimen is once a day administration. Currently, Clarithromycin is administered twice daily in the form of commercially available immediate release compositions. Clarithromycin is practically insoluble in water and shows pH dependent solubility profile. The  
15      solubility significantly increases at lower pH values (I. I. Salem, Analytical Profiles of Drug Substances and Excipients, Volume 24, Academic Press, (1996) at 46-85)

Clarithromycin undergoes degradation in acidic medium. It degrades rapidly at normal gastric pH of 1.0-2.0 (P.O. Erah et. al., J. Antimicrob. Chemother. 39, 5-12, (1997)). On the market, Clarithromycin is present in the form of film coated tablets, a suspension and extended-release tablets.

Various compositions with extended-release characteristics are known in the art for example, Horder et al. (U.S. Pat. No. 4,842,866), disclose a slow release composition comprising sodium alginate, sodium-calcium alginate and a  
25      therapeutically effective ingredient.

Broad et al. (U.S. Pat. No. 5,705,190) disclose a controlled release solid pharmaceutical compositions adopted for oral administration comprising a water soluble alginate salt, a complex salt of alginic acid, wherein the cation is selected from the group consisting of calcium, strontium, iron or barium, and an organic  
30      carboxylic acid to facilitate dissolution of basic drug. These formulations are said to be suitable for once a day administration. The release rate of the

Clarithromycin is controlled using a matrix based on a water-soluble alginate salt and a complex salt of alginic acid.

The release model of a drug from calcium alginate matrices has been shown to be highly dependent on the release medium. Cross-linking calcium 5 ions were rapidly discharged from the matrices in the presence of acid and affected the ability to provide delayed drug release. (Ostberg, T. et. al., Int. J. Pharm. 112, 241-248 (1994)). It appears that such interactions may lead to inconsistent and unpredictable drug release upon administration of alginate based controlled drug delivery devices.

10 Al-Razzak et al. (U.S. Pat. No. 6,010,718) disclose a pharmaceutical composition for extended release of an erythromycin derivative in a gastrointestinal environment. The composition includes an erythromycin derivative and a hydrophilic water-soluble polymer. The polymer is selected from group consisting of polyvinyl pyrrolidone, hydroxypropyl cellulose, 15 hydroxypropylmethyl cellulose, methyl cellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers and derivatives and mixtures.

Compositions based on hydrophilic water-soluble polymers commonly exhibit an initial "burst effect" which causes a non-linear release rate of a drug. 20 (See, e.g., U.S. Patent No. 5,419,917.) Polymers such as hydroxypropylmethyl cellulose can be hydrated at low pH levels to form a viscous gel layer that controls drug release. During drug release, at high pH levels, however the tablets become smaller and smaller due to polymer erosion. The size reduction leads to a reduction in the surface area that may affect the dissolution rate. (See 25 U.S. Pat. No. 5,695,781.)

The processing of these hydrophilic water-soluble polymers such as hydroxypropylmethyl cellulose, is difficult and requires strict controls. For example, Koji et al. (JP 09095440) disclose a lyophilized composition of a fluid mixture of medicine and hydrogel forming polymer (such as hydroxypropyl 30 cellulose, and hydroxypropylmethyl cellulose). The Koji composition is said to float in the stomach and release a medicament slowly.

Gel forming cellulose ethers (e.g., hydroxypropyl cellulose and hydroxypropylmethyl cellulose) have been used in controlled release of drug delivery to preparing matrix systems. However, the mechanism of release from these matrices depends on the aqueous solubility of the drug and the hydrophilicity of 5 the polymer used. (A. G. Thombre & J. R. Cardinal in Encyclopedia of Pharmaceutical Technology, Volume 2, 1990, 61-88).

Lek (WO 00/48607) discloses a formulation including Clarithromycin or a derivative and a mixture of fatty and hydrophilic components. The formulation also includes a surfactant and pH modulator, along with other pharmaceutically 10 acceptable additives. An acid resistant coating on the tablet formulation has been disclosed.

Insoluble polymers such as ethyl cellulose (EC) have been used for controlling the release of therapeutic agents from drug delivery devices. For example, ethyl cellulose has been used extensively as a coating layer for dosage 15 forms to control the release of a therapeutic agent. However, ethyl cellulose is insoluble at gastrointestinal pH. Therefore, the drug release depends upon the permeability of the EC films. The aqueous fluids penetrate and dissolve the drug, which can diffuse out from the dosage form. The rate of release is dependent upon the drug solubility in the gastrointestinal environment. Thus, 20 the coatings may provide a formulation having a pH dependent release rate and variability in the release rate of drugs that are insoluble at gastrointestinal pH. Moreover, the coating process requires a controlled operation because a variation in the thickness of the coating on the composition can lead to variation in drug release.

Attempts have been made to incorporate ethyl cellulose in sustained 25 release matrix. Radebaugh et al. (U.S. Pat. No. 5,462,747) disclose a process for preparing a composition of a pharmaceutically active agent for sustained release, in the form of shaped tablets or tablet layers, characterized by a long lasting slow and relatively regular incremental release of a the active agent upon 30 administration. The composition includes a granulating agent such as povidone, a polymer such as ethyl cellulose, a wicking agent such as microcrystalline

and/or otherwise requires special equipment, processes or excipients. According to the process of the invention, the therapeutic agent is converted to a dosage form having optimum characteristics and can be readily employed for the compositions of the invention.

5

#### DETAILED DESCRIPTION OF THE INVENTION

In the context of the present invention a number of terms have been used. In order to provide a clear and consistent understanding of the specification, claims and the scope, the following definitions are provided. Where specifically 10 not indicated the terms used herein are used according to their normal and or art recognized meaning.

"Controlled release" as used herein, means sustained release or slow release or modified release or prolonged release or extended release or other similar terms used to indicate a composition providing an extended profile of 15 drug release from the composition when exposed to aqueous environment either in-vitro or in-vivo as compared to an immediate release composition.

"Poorly soluble or poor solubility" as used herein, has the same meaning as is described in U.S. Pharmacopoeia XXIV and is used interchangeably with slightly soluble. Typically, a slightly soluble compound has a solubility of about 20 1 part in about 30 parts of water. (Further, a saturated solution of a slightly soluble compound in water can have a concentration of from about 1 mM to about 100 mM of the compound or a saturated solution and an insoluble of a compound in water can have a concentration of less than about 1 mM.)

"Acid susceptible compounds" as used herein, refers to compounds or 25 active agents that degrade when allowed to contact an acidic environment such as acidic gastric juices.

"Therapeutic agent, active agent or drug" as used herein, have been used interchangeably and have the meanings recognized by one skilled in the art.

The therapeutic agent is a macrolide antibacterial agent. Specific 30 macrolide antibacterial agents include compounds such as, for example,

In one aspect the invention provides a controlled release pharmaceutical compositions for an acid labile, poorly soluble therapeutic agent, exhibiting pH dependent solubility characteristics when exposed to aqueous environment.

5 In another aspect the present invention provides a controlled release composition and simple method for preparing a controlled release composition for macrolide antibacterial agents such as, for example, Clarithromycin salts and derivatives thereof.

10 In another aspect the present invention provides a convenient dosage form for Clarithromycin, a pharmaceutical salt or a derivative thereof that facilitates patient compliance.

15 Yet another aspect the present invention provides a process for making a controlled release compressed dosage form such as tablet, pill, or caplet of a therapeutic agent when present in a physical form is difficult to compress or has poor flow or results in said dosage forms having poor physical characteristics like friability or defects like capping or lamination which otherwise requires special equipments or excipients to produce said dosage forms. The therapeutic agent is selected from group comprising of macrolide group of antibacterial agents such as clarithromycin.

20 **SUMMARY OF THE INVENTION**

25 The present invention provides a controlled release pharmaceutical composition that includes a therapeutic agent having poor solubility in aqueous environment such as, for example, a macrolide antibacterial. The composition includes a mixture of the therapeutic agent, a water insoluble polymer, and optionally an optimizing agent. In addition, the composition can also include fillers, binders, and other additives. The invention also provides a process for converting a therapeutic agent, having poor tableting characteristics, into a controlled release solid dosage form.

30 Often the formation of dosage forms such as tablets having therapeutic agents present in a physical form having poor tableting characteristics results in

cellulose, erosion promoter such as pregelatinized starch to form a granulation. The granulation is then blended with a composition of an active agent an erosion promoter, wicking agent, lubricant, glidant before compressing into tablet. The goal of the '747 patent is said to be a long lasting and relatively regular 5 incremental release of the pharmaceutically active agent upon administration. The release has been shown to be pH independent. The amount of EC is from 3-12 parts by weight of total non-active components of tablet. The pharmaceutically active agent is selected from various therapeutic categories.

Eichel et al. (U.S. Pat. No. 5,478,573) describe a delayed, sustained-  
10 release pharmaceutical preparation including a core of a drug such as propranolol hydrochloride surrounded by a hydrated diffusion barrier having thickness of at least 20 microns, comprising of film forming polymer mixture of an acrylic resin and ethyl cellulose. In one embodiment an acrylic resin such as Eudragit RS 30D and RL 30D are mentioned. The core drug is preferably a  
15 water-soluble drug. The thickness of the barrier layer is such that less than 5% of drug dissolves within 2 hours of administration.

Clarithromycin is very soluble in the stomach and fairly soluble in the upper region of small intestine where absorption is most likely to occur. As the drug's solubility decreases in the lower intestine, less drug is available for  
20 absorption. (See, e.g., U.S. Pat. No. 5,705,190.) Usually the time required for such type of composition to pass through distal end of small intestine is 6 to 8 hrs.

Thus, a continuing need exists for compositions capable of delivering therapeutic agents, such as, for example, Clarithromycin in at a rate sufficient to  
25 provide a beneficial effect, wherein the maximum delivery of the therapeutic agent will be within the 6-8 hour absorption window.

There is a need for a controlled drug delivery devices, such as, tablets, caplets, capsules, and the like, for delivery of therapeutic agents, which are capable of offering the advantages associated with a controlled drug delivery  
30 device while maintaining the desired bioavailability after administration.

clarithromycin, erythromycin, azithromycin, dirithromycin, roxithromycin, derivatives thereof and pharmaceutically acceptable salts thereof. Preferably the macrolide antibacterial agent is clarithromycin, derivatives thereof or a pharmaceutically acceptable salt thereof.

5 Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids, which form a physiological acceptable anion, for example, tosylate, methanesulfonate, malate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate,  $\alpha$ -ketoglutarate, and  $\alpha$ -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, 10 nitrate, bicarbonate, and carbonate salts.

15 Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be 20 made.

The amount of clarithromycin in the composition can vary from about 30% to about 75% by weight of the composition. Preferably the composition comprises about 40 to about 65% by weight of the clarithromycin salt or derivative. Most preferably the therapeutic agent comprises about 45 to about 25 60% of the clarithromycin salt or derivative.

The insoluble polymers useful in the invention are pharmaceutically acceptable polymers, such as, for example, water insoluble cellulosic derivatives, polyvinyl chloride, amino alkyl methacrylates and the like. Suitable water insoluble cellulose derivatives include polymers such as, for example, ethyl cellulose having a viscosity grade 7 cps, ethyl cellulose having a viscosity grade 10 cps, ethyl cellulose having a viscosity grade 20 cps, ethyl cellulose having a viscosity grade 100 cps.

Commercially available examples of ethyl cellulose compositions include 30 products such as, for example, Surelease<sup>TM</sup>, Aquacoat<sup>TM</sup> and mixtures thereof.

Examples of such commercially available ethyl cellulose grades are Ethocel 7 cps, Ethocel 10 cps, Ethocel 20 cps and Ethocel 100 cps from Dow, Ltd. USA. Preferably the ethyl cellulose polymer is ethyl cellulose 7 cps and ethyl cellulose 10 cps. The most preferred ethyl cellulose polymer is ethyl cellulose 7 cps or a mixture of ethyl cellulose 7 cps and ethyl cellulose 10 cps.

5 The amount of the insoluble polymer in the composition is at least about 5 % based on the total weight of the therapeutic agent present in the composition. Preferably, the insoluble polymer is from about 10 to about 40%. More preferably, the amount of polymer is from about 15% to about 35% of the 10 amount of the therapeutic agent present in the composition. Most preferably, the amount of polymer is from about 20% to about 30% of the amount of therapeutic agent present in the composition.

15 The viscosity grade and amount of polymer present in composition can affect the release profile of the drug from the composition. Depending upon the desired drug release profile and drug characteristics, a mixture of one or more viscosity grades of polymer may be employed. Thus, adjustments with respect to polymer present in the composition may be made and are within the scope of the present invention.

20 The composition of the invention further comprises additives that can be used to modify the desired release profile of the therapeutic agent in the composition or the invention.

25 The present invention overcomes the problem of forming tablets with therapeutic agents that have poor tableting characteristics by incorporating an "optimizing agent" in the composition. Optimizing agents useful in practicing the present invention are lactose, dicalcium phosphate, calcium phosphate and polymethacrylates such as anionic polymers of methacrylic acid and methacrylate esters, cationic polymer with dimethyl aminoethyl ammonium functional group and mixtures thereof. Examples of suitable polymethacrylates such as anionic polymers of methacrylic acid and methacrylate esters, are 30 disclosed in U.S. Patent No. 5,292,522 ("the '522 patent"). The '522 patent discloses polymers comprising acrylic acid, methacrylic acid, alkyl esters of

these acids and amino alkyl esters of these acids. These copolymers are commercially available from Rohm Pharma GmbH under the tradename Eudragit®. Preferably the "optimizing agent" is a combination comprising a polymer of methacrylic acid and methyl methacrylate and a compound selected 5 from the group consisting of lactose, dicalcium phosphate and tricalcium phosphate or a mixture thereof.

Preferably the composition comprises from about 10 to about 90% of the optimizing agent relative to the amount of therapeutic agent of the invention. More preferred are compositions wherein the "optimizing agent" is present from 10 about 20 to about 60% of optimizing agent relative to the amount of therapeutic agent in the composition.

The compositions of the invention further comprise an optional binding agent. The preferred binding agents suitable for practicing the invention are low viscosity water soluble cellulose derivatives such as hydroxypropyl cellulose, 15 hydroxyethyl cellulose, sodium carboxymethyl cellulose, alginic acid derivatives, polyvinyl pyrrolidone, soluble starches or mixtures thereof. A preferred binding agent is HPMC, PVP or mixtures thereof. Preferably the binding agent comprises from about 1 to about 10 %. Preferably, the binding agent is from about 1 to about 4% by weight of the composition.

20 In addition to the above ingredients, the compositions of the invention may further comprise fillers such as microcrystalline cellulose, mannitol, sorbitol, starches and the like, including mixtures thereof as are well known in the art. Preferably fillers are present in an amount of from 0% to about 50% by weight, either alone or in combination. More preferably they are present from 25 about 5% to about 20% of the weight of the composition.

However, the amount of fillers can be adjusted in order to render the composition suitable for converting into a pharmaceutical dosage form without affecting the efficacy of the compositions of the invention. The compositions, when presented in the form of a solid dosage form may further comprise 30 additives like lubricants, glidants, antiadherents such as stearates, stearic acid,

talc, silicon dioxide and mixtures thereof. When present these additives comprise from 0 to about 5% by weight either alone or in combination.

5        Optionally the composition may further comprise additives known in the art such as, buffering agents such as, for example, citrates, carbonates, and the like; or surface active agents such as, for example, polysorbates, poloxamers and the like.

10      The additives included in the compositions of the invention may be added in amounts that are required to produce desired function of additive in order to administer the composition in the form of dosage form as are known in the art. The amounts and types of additives useful in the compositions of the invention are well known to those skilled in the art.

15      The compositions can be administered orally in the commonly known dosage forms in the art. The tablets, caplets, or pills suitable for oral administration can be prepared using standard tabletting machines known in the art, which have appropriately sized dies. Compressed or molded solid dosage forms such as tablets, caplets, and pills are preferred. However, for the purpose of the present invention, any dosage forms suitable for administration of the composition of the invention, e.g., capsules and the like, are within the scope of the invention.

20      In other aspect of the invention provides a process for making an extended release composition by granulating and compressing a therapeutic agent, wherein the agent has a physical form that is poorly compressible, or other difficulties in compression. Some of the difficulties include tablets, etc., which have poor characteristics, such as capping, lamination, and/or high friability when compressed. According to the process of the invention, the therapeutic agent is mixed with a water insoluble polymer, and an optimizing agent as described herein.

25      The mixing of the ingredients is achieved with blenders (or mixers) that are commonly used in the pharmaceutical art such as, for example, a cone blender. The other additives, such as fillers or optional additives are added to

the mixture prior to a final mixing. The order of addition of additives is not critical to the invention. Further, the process involves making granules of the mixture, prepared as described above, with a binding agent such as those described herein. According to the process the most preferred solvent for the 5 binding agent is water. However, any other pharmaceutically acceptable solvent may be employed.

The blend may be granulated using methods that are known in the art, such as high shear or low shear granulators, mixers, and fluid bed granulators. The wet granules are ultimately dried, suitably sized by the techniques that are 10 known in the art. The granules are blended with optional additives such as lubricants, glidants, antiadherents that are known in the art. Most preferably the additives are selected from group comprising of stearic acid or stearates, talc, silicon dioxide either alone or in combination. The final blend is then converted into tablets or a suitable solid dosage form by employing equipment such as 15 tableting machines, which are known in the art.

Optionally the composition may be coated by film forming polymers and methods as are known in the art without significantly altering the objects of the inventions.

The following examples are intended to illustrate the invention without 20 limiting the scope of the invention:

Example 1 – Preparation of Formulation & Drug Release Data

Ingredient Nos. 1 to 5 were blended. Purified water was added to 25 granulate the blend. The granules were dried in a tray dryer at 60±2°C. The dried granules were then passed through 20 mesh sieve. The granules were then blended with ingredient no. 7, 8, and 9. Finally they were compressed into tablets. The resultant tablets could be readily compressed and had the desired physical characteristics. A single formulation was prepared according to the general method described above. The composition of the formulation is provided in Table 1.

Table I

No.	Ingredient name	% w/w **
1.	Clarithromycin [d(0.5) = 37.7 $\mu$ m]	57.3
2.	Ethyl cellulose 7 cps	14.3
3.	Dicalcium phosphate	17.2
4.	Eudragit L-100-55	5.7
5.	Hydroxypropyl cellulose	2.9
6.	Magnesium stearate	1.0
7.	Talc	1.0
8.	Colloidal silicon dioxide	0.6
9.	Purified water*	q.s.

\* Evaporates during processing.

\*\* Values rounded off.

5

In-vitro dissolution studies were carried out using a buffered media of pH 5.0. Using USP Type II apparatus. The percent drug released is shown in Table II.

Table II

10

Time (Hours)	% Drug Released pH 5.0
1	13.3
2	22.4
3	30.5
4	37.8
6	52.0
8	66.0

#### Example 2 - Preparation of Formulation & Drug Release Data

Ingredient Nos. 2 to 5 were blended in a cone blender. Resultant mixture was blended with ingredient no. 1. The blend obtained was granulated with

aqueous dispersion of Kollidon K-30 in a low shear mixer. The granules obtained were dried until the loss on drying was less than 1.0%. The granules were blended with ingredient no. 7, 8, & 9 before compressing into caplets. The composition of the formulation is provided in Table III.

5

Table III

No.	Ingredient name	% w/w **
1.	Clarithromycin (<180 $\mu$ m)	57.3
2.	Ethyl cellulose 7 cps and Ethyl cellulose 10 cps (8:2)	14.3
3.	Dicalcium phosphate	13.7
4.	Lactose	3.4
5.	Eudragit L-100-55	5.7
6.	Kollidon K-30 (10% aqueous dispersion)	2.9
7.	Magnesium stearate	1.0
8.	Talc	1.0
9.	Colloidal silicon dioxide	0.6

\*\* Values rounded off.

10 Dissolution profile was studied in buffered medium of pH 5.0. The percent drug released is shown in Table IV.

Table IV

Time (Hours)	% Drug Released pH 5.0
1	13.1
2	21.5
3	29.5
4	36.0
6	48.8
8	60.8
10	71.6
12	81.3
14	90.2

The finished composition, in the form of tablets or caplets, was evaluated  
 5 for their physical parameters. The tablets did not show sign of unwarranted compression defects, had friability values in the range of 0.05 to 0.5% by weight. The caplets or tablets had acceptable appearance without the need for extraneous coatings.

10 Example 3 – Bioequivalence Study

In another composition prepared as described in Example 2 was subjected to a controlled two way crossover bioequivalence study and compared with reference product Biaxin® XL (Abbott Laboratories, USA) where ratio for LN Cmax and LN AUC<sub>0-inf</sub> was found to be in compliance with the requirement.  
 15 The composition of the formulation is provided in Table V

The ratio of LN Cmax was 0.96 and the ratio of LN AUC<sub>0-inf</sub> was 1.00.

Table V

No.	Ingredient Name	%w/w
1	Clarithromycin	59.74
2	Ethyl cellulose, 7 cps	9.56
3	Dicalcium phosphate	17.92
4	Methacrylic acid copolymer	5.97
5	PVP K-30	4.48
6	Magnesium stearate	0.72
7	Talc	1.02
8	Colloidal silicon dioxide	0.60
9	Opadry Y-1-7000	20 mg/Tab

All cited publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

## What is claimed is

1. A pharmaceutical composition for controlled release of an active agent having antibiotic activity comprising a mixture of a macrolide antibacterial agent, and a water insoluble polymer.
2. The composition of claim 1, wherein the macrolide antibacterial agent is clarithromycin, erythromycin, azithromycin, dirithromycin, roxithromycin, a derivative or a pharmaceutically acceptable salt thereof.
3. The composition of claim 2, wherein the macrolide antibacterial agent is clarithromycin.
4. The composition of any of claims 1-3, further comprising an optimizing agent.
5. The composition of any of claims 1-4, further comprising a binder.
6. The composition of any of claims 1-5, wherein the particle size of the macrolide antibacterial agent is less than 180  $\mu\text{m}$ .
7. The composition of any of claims 1-6, wherein the water insoluble polymer is a water insoluble cellulose derivative.
8. The composition of claim 7, wherein the cellulose derivative is ethyl cellulose.
- 20 9. The composition of claims 7 or 8, wherein the ethyl cellulose has a viscosity grade of 7 cps, 10 cps, 20 cps or 100 cps or mixtures thereof.
10. The composition of claim 9, wherein the ethyl cellulose has a viscosity grade of 7 cps or 10 cps.
11. The composition of claim 10, wherein the ethyl cellulose is a mixture of ethyl cellulose having a viscosity grade of 7 cps and 10 cps.
- 25 12. The composition of any of claims 1-11, wherein the amount of water insoluble polymer is at least about 5 % by weight.

13. The composition of claim 12, wherein the amount of insoluble polymer is from about 10 to about 40%.
14. The composition of claim 13, wherein the amount of insoluble polymer is from about 15% to about 35%.
- 5 15. The composition of claim 14, wherein the amount of insoluble polymer is from about 20% to about 30%.
16. The composition of any of claims 1-4, wherein the optimizing agent comprises a polymer of methacrylic acid, methacrylate ester or a mixture thereof.
- 10 17. The composition of claim 16, wherein the optimizing agent comprises a co-polymer of methacrylic acid and a methacrylate ester.
18. The composition of claim 17, wherein the optimizing agent further comprises an additive such as lactose, dicalcium phosphate and tricalcium phosphate or a mixture thereof.
- 15 19. The composition of claim 18, wherein the additive comprises dicalcium phosphate.
20. The composition of any of claims 1-5, wherein the binder is a water soluble cellulose derivative, polyvinyl pyrrolidone or mixture thereof.
21. The composition of claim 1, wherein the composition is a solid oral dosage form.
- 20 22. The composition of claim 21, wherein the dosage form is a tablet, pill, caplet, pellet or granule.
23. The composition of claim 22, wherein the dosage form is a capsule comprising pellets or granules.
- 25 24. The composition of claim 21, wherein the dosage form comprises a coating.

25. A process for preparing a pharmaceutical composition of claim 1, comprising mixing a macrolide antibacterial therapeutic agent, with a water insoluble polymer.
26. The process of claim 25, wherein the macrolide antibacterial agent is selected from the group consisting of clarithromycin, erythromycin, azithromycin, dirithromycin, roxithromycin, derivative or a pharmaceutically acceptable salt thereof.
27. The process of claim 26, wherein the macrolide antibacterial agent the macrolide antibacterial agent is clarithromycin.
- 10 28. The process of any of claims 25-27, further comprising an optimizing agent.
29. The process of any of claims 25-27, further comprising a binder.
30. The process of any of claims 25-27, wherein the particle size of the therapeutic agent is less than 180  $\mu\text{m}$ .
- 15 31. The process of any of claims 25-31, wherein the water insoluble polymer is a water insoluble cellulose derivative.
32. The process of claim 31, wherein the cellulose derivative is ethyl cellulose.
33. The process of claim 32, wherein the ethyl cellulose has a viscosity grade of 7 cps, 10 cps, 20 cps or 100 cps or mixtures thereof..
- 20 34. The process of claim 33, wherein the ethyl cellulose has a viscosity grade of 7 cps or 10 cps.
35. The process of claim 34, wherein the ethyl cellulose is a mixture of ethyl cellulose having a viscosity grade of 7 cps and 10 cps.
- 25 36. The process of claim 25, wherein the amount of water insoluble polymer is at least about 5 % by weight.

37. The process of claim 36, wherein the amount of insoluble polymer is from about 10 to about 40 %.
38. The process of claim 37, wherein the amount of insoluble polymer is from about 15% to about 35 %.
- 5 39. The process of claim 38, wherein the amount of insoluble polymer is from about 20% to about 30 %.
40. The process of any of claims 25-27, wherein the optimizing agent comprises a polymer of methacrylic acid, polymethacrylates or a mixture thereof.
- 10 41. The process of claim 40, wherein the optimizing agent further comprises an additive such as lactose, dicalcium phosphate and tricalcium phosphate or a mixture thereof.
42. The process of claim 41, wherein the additive comprises dicalcium phosphate.
- 15 43. The process of claim 25, wherein the composition is a solid oral dosage form.
44. The process of claim 43, wherein the dosage form is a tablet, pill, caplet, pellet or granule.
45. The process of claim 25, wherein the therapeutic agent, and water
- 20 insoluble polymer are blended by wet granulation.

## INTERNATIONAL SEARCH REPORT

Int'l	International Application No
PCT/IB 02/04593	

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	A61K9/16	A61K9/26	A61K9/52	A61K9/54	A61K31/7048
	A61K31/7052	A61P31/04			

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 5 082 656 A (HUI HO-WAH ET AL) 21 January 1992 (1992-01-21)</p> <p>column 1, line 59 -column 2, line 13 examples I-XXIII claims 1-11</p> <p>—</p> <p>-/-</p>	<p>1-3, 7, 8, 12-15, 25-28, 31, 32, 36-39</p>

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

- \*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the International search

13 February 2003

Date of mailing of the International search report

20/02/2003

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Economou, D

## INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 02/04593

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 62229 A (ADVANCED PHARMA INC) 30 August 2001 (2001-08-30)  page 10, paragraph 3 - paragraph 5 page 11, line 9 - line 11 page 19; example 22 page 21; example 37 page 22; example 49	1-5,7,8, 12-18, 21-29, 31,32, 36-41, 43-45
X	EP 1 064 942 A (FUJISAWA PHARMACEUTICAL CO) 3 January 2001 (2001-01-03) page 2, line 24 - line 35 page 8, line 35 - line 51 page 9, line 16 - line 46 examples 16-21 claims 1,2,10,15,18,19	1-45
P,X	WO 02 24174 A (GALEPHAR M F ;SERENO ANTONIO (BE); BAUDIER PHILIPPE (BE); VANDERBI) 28 March 2002 (2002-03-28) page 9, line 1 -page 10, line 5	1-5,7,8, 16,17, 20-24

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.2

Claims Nos.: 1-6,12-30,36-45 (all partially)

Present claims 1-24 relate to an extremely large number of possible products. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the products claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to products comprising a macrolide antibacterial agent and a water insoluble cellulose derivative (particularly ethyl cellulose) and to the corresponding processes of manufacture (claims 25-45)

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB 02/04593

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: 1-6, 12-30, 36-45 (all partially) because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.